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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/700,565	07/25/96	GRUENBERG M	6870-500B

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EXAMINER	
SCHWADRON, R	

ART UNIT	PAPER NUMBER
1644	23

DATE MAILED: 01/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/700,565	Gruenberg
Examiner	**Group Art Unit**
Ron Schwadron, Ph.D.	1644

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17, 22-35, and 154-210* is/are pending in the application.

Of the above, claim(s) *1-17, 30, and 154-210* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-29 and 31-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Applicant's election with traverse of the species (1) the method of claims 22-35 and (2) Th1 cells in Paper No. 22 is acknowledged. The traversal is on the ground(s) that are stated in said paper. This is not found persuasive because of the following reasons. Regarding applicants comments, subsequent to the Office Action mailed 11/21/97 there have been five amendments that have added or changed the claims under consideration. There have also been three supplemental IDSs that have been filed. The aforementioned have necessitated a new search of the prior art. Regarding applicants comments, the method of species C differs from that of species A and E in that the method of species A and E prohibits the use of exogenous IL-2, while the use of exogenous IL-2 is encompassed by the method of species C. The methods of species E, B and C differ in that species E requires treatment with two or more activating proteins, species B encompasses treatment with nonprotein activating agents, while species C requires treatment with one or more activating proteins. It would require an undue burden for the Examiner to search the ever growing number of different species of methods present in the instant application. Applicants comments regarding June et al. are addressed in prior art rejections present in the instant Office Action. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-17,154-210,30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, the requirement having been traversed in Paper No. 6.

3. Claims 22-29,31-35 are under consideration.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-29,31-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "at least about 10^9 cells/liter" in the context of the method of claim 22. Regarding applicants comments, original claim 150 refers to cells made by the method of claim 1 (eg. not the method of claim 22) and also refers a composition of a volume of "1 liter or less" with "at least about 10^9 cells". There is no support in the specification as originally filed for the scope of the claimed invention (eg. the claimed invention constitutes new matter).

6. Claims 22-29,31-35 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive

Claim 22 is indefinite in the recitation of "regulatory T lymphoid cells" because it is unclear what this means or encompasses. The specification on page 19 discloses that "a regulatory immune cell is any mononuclear cell with a defined cytokine production profile in which such cytokine profile does not directly mediate an effector function" and that said cell "has the ability to control or direct an immune response, but does not act as an effector cell in the response". However, it is unclear what this means or encompasses. While the specification discloses that Th1 or Th2 are "regulatory immune cells", the art recognizes that said cells are effector cells with regards to the pathogenesis of a variety of different autoimmune diseases (see Liblau et al., pages 34-38). For example, Liblau et al. teach that Th1 cells are involved in the pathogenesis of IDDM wherein said cells bind islet antigens via TCR mediated antigen specific recognition of said islet antigens (see page 35, first column penultimate paragraph). Liblau et al. teach that the lymphokines secreted by said cells are involved in the pathogenesis of IDDM. Thus, according to the definition in the specification Th1, Th2 or Th3 are not "regulatory immune cells" because they function as effector cells and the cytokines they produce also function in a variety of different effector mechanisms. It is unclear as to what cell population is encompassed by this term and it is unclear what the aforementioned definition actually means.

Regarding applicants comments, applicant states that according to the specification that "regulatory" versus "effector" cells can be distinguished by the ability of effector cells to "directly eliminate pathogens or tumor cells" (amendment filed 5/27/98, page 28). However,

Mosmann et al. (Immunology Today, 1996) teach that Th1 (a form of regulatory cell as defined in the specification) secrete lymphotoxin (see Table 1), wherein the art recognizes that lymphotoxin is directly cytotoxic to viruses and tumor cells (see Arai et al., columns 1 and 2). Thus, said Th1 can directly eliminate pathogens or tumor cells via secretion of lymphotoxin. Therefore, it is unclear as what "regulatory" cell means or encompasses because while applicant argues that "regulatory" versus "effector" cells can be distinguished by the ability of effector cells to "directly eliminate pathogens or tumor cells", the art recognizes that "regulatory" cells such as TH1 also can directly eliminate pathogens or tumor cells. Thus it is unclear as to what distinguishes a regulatory T cell from an effector T cell.

Claim 22 is indefinite in the recitation of "clinically relevant" because it is unclear what this means or encompasses. The specification discloses that " clinically relevant" in the context of the claimed method means methods for producing typically greater than 10^9 or 10^{10} cells, but does not specifically define what clinically relevant numbers of cells means in the context of the claimed method. For example, it is unclear whether a method which produced 10^8 cells would qualify as a method for producing clinically relevant numbers of cells, because it is unclear as to what number of cells is the lowest number of cells that constitutes "clinically relevant" in the context recited in the claim.

Regarding applicants comments, the claimed invention is not drawn to a composition containing a clinically relevant number of immune cells, it is drawn to a method of generating cells. It is unclear what "clinically relevant cell numbers means in the context recited in the claimed invention. In fact, according to applicants comments on page 30 of the amendment filed 5/27/98, said term can have a different meaning when used in a method versus composition claim. Regarding applicants comments about the specification, page 21, in view of the fact that "clinically relevant cell numbers" is not defined in the specification in terms of "therapeutically effective" number of cells, it is unclear as to the relationship of said term to the definition of "clinically relevant cell numbers" in the context of the claimed method.

7. Regarding priority for the claimed inventions with regards to the application of prior art, the claimed inventions are not disclosed in parent application provisional application 60/044693 (the application formerly known as 08/506668), and therefore priority with regards to the application of prior art is taken as the filing date of PCT WO 97/052349 to which applicant claims

priority. For example, there is no disclosure in 60/044693 of the method of claim 22 for generating " regulatory T lymphoid cells" per se (60/044693 refers to methods of generating autologous effector T lymphoid cells). Regarding applicants comments, there is no disclosure in parent application provisional application 60/044693 of the term "regulatory T lymphoid cells" or a method of producing such cells. There is no disclosure in 60/044693 of the method of claim 22, parts b and c.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 22-28,31,32,34,35 are rejected under 35 U.S.C. 102(b) as being anticipated by June et al. (WO 94/29436).

Regarding the term "regulatory T lymphoid" cells, while it is unclear what said term means or encompasses, in the instant rejection said term will be addressed as encompassing Th1 cells. June et al. teach the method of claim 22, wherein unfractionated T cells or CD4+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody or IL-2 treatment wherein said cells are expanded to at least about 10^9 cells per liter (see abstract, pages 4-9,13, claims 1-28,30-37). Figures 1 and 2 show experimental data indicating the expansion of cells to numbers greater than 10^{10} cells. June et al., page 27, indicates that the cells were maintained at a concentration of 10^6 cells/ml (eg. 10^9 cells/liter). June et al. teach that said cells were treated with IL-2 (eg. see Table 2). It is an inherent property of said treatment that it leads to the development of Th1 (eg. see claim 28). The cells produced by the method of June et al. include Th1 (eg. as defined by production of IFN-γ (see Table 2)). Thus, it is an inherent property of the method taught by June et al. that Th1/ Th1 like cells are produced. June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific cells (see page 9, first complete paragraph) and that said cells can be purified (see pages 29 and 300). T cells are by

definition specific for a defined antigen (eg. the antigen bound by the TCR expressed by said T cell). The method of June et al. can use treatment with anti-CD3 and antiCD28 antibodies to generate Th1 cells (eg. see Table 2, wherein said cells produce IFN-γ).

Regarding applicants comments, June et al. teach the production of Th1 cells (eg. CD4+ T cells which produce IFN-γ, see Table 2). Regarding applicants comments about Example 6, said example clearly shows the production of a mixed population of CD4+ cells which contains Th1 cells (eg. CD4+ T cells which produce IFN-γ, see Table 2). The cell population clearly is predominately Th1 after the first stimulation cycle (see S1, Table 2) and then includes numbers of Th2 cells in subsequent stimulation cycles (see Table 2). Furthermore, it is an inherent property of said method that Th1 are produced because claim 28 discloses that IL-2 treatment of T lymphoid cells (as per disclosed by June et al.) leads to the production of Th1 cells. June et al. teach the method of claim 22, wherein unfractionated T cells or CD4+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody or IL-2 treatment wherein said cells are expanded to at least about 10^9 cells per liter (see abstract, pages 4-9,13, claims 1-28,30-37). Figures 1 and 2 show experimental data indicating the expansion of cells to numbers greater than 10^{10} cells. June et al., page 27, indicates that the cells were maintained at a concentration of 10^6 cells/ml (eg. 10^9 cells/liter).

10. Claims 22-28,31,32,34,35 are rejected under 35 U.S.C. 102(e) as being anticipated by June et al. (US Patent 5,858,358).

Regarding the term "regulatory T lymphoid" cells, while it is unclear what said term means or encompasses, in the instant rejection said term will be addressed as encompassing Th1 cells. June et al. teach the method of claim 22, wherein unfractionated T cells or CD4+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody or IL-2 treatment wherein said cells are expanded to at least about 10^9 cells per liter (see abstract, Figures 1-3, columns 4-29). Figures 1 and 2 show experimental data indicating the expansion of cells to numbers greater than 10^{10} cells. June et al., column 23, indicates that the cells were maintained at a concentration of 10^6 cells/ml (eg. 10^9 cells/liter). June et al. teach that said cells were treated with Il-2 (eg. see Table 2). It is an inherent property of said treatment that it leads to the development of Th1 (eg. see claim 28 of the instant application). The cells produced by the method of June et al. include Th1 (eg. as

defined by production of IFN-γ (see Table 2)). Thus, it is an inherent property of the method taught by June et al. that Th1/ Th1 like cells are produced. June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific cells (see columns 8 and 9) and that said cells can be purified (see columns 25-28). T cells are by definition specific for a defined antigen (eg. the antigen bound by the TCR expressed by said T cell). The method of June et al. can use treatment with anti-CD3 and antiCD28 antibodies to generate Th1 cells (eg. see Table 2, wherein said cells produce IFN-γ).

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 22-28,31-35 are rejected under 35 U.S.C. § 103 as being unpatentable over June et al. (WO 94/29436) or June et al. (US Patent 5,858,358) in view of Cracauer et al. (US Patent 4,804,628).

Regarding the term "regulatory T lymphoid" cells, while it is unclear what said term means or encompasses, in the instant rejection said term will be addressed as encompassing Th1 cells. June et al. teach the method of claim 22, wherein unfractionated T cells or CD4+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody or IL-2 treatment wherein said cells are expanded to at least about 10^9 cells per liter (see abstract, pages 4-9,13, claims 1-28,30-37). Figures 1 and 2 show experimental data indicating the expansion of cells to numbers greater than 10^{10} cells. June et al., page 27, indicates that the cells were maintained at a concentration of 10^6 cells/ml (eg. 10^9 cells/liter). June et al. teach that said cells were treated with IL-2 (eg. see Table 2). Said treatment leads to the development of Th1 (eg. see claim 28). The cells produced by the method of June et al. include Th1 (eg. as defined by production of IFN-γ (see Table 2). June et al. do not teach the use of a hollow fiber bioreactor in said method. Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro (see columns 1-3). It would have been prima facie obvious to one of ordinary skill in the

art at the time the invention was made to have created the claimed invention because June et al. teach the claimed method except for the use of a hollow fiber bioreactor and Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro. One of ordinary skill in the art would have been motivated to do the aforementioned because Cracauer et al. teach that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in culture."(column 1).

Regarding applicants comments about June et al., said comments are addressed in paragraph 9 of this Office Action. Regarding applicants comments about Cracauer et al., there is no evidence of record that the fiber bioreactor taught by Cracauer et al. could not be used in the claimed invention. Cracauer et al. teaches that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in vitro". While applicant has speculated that the device taught by Cracauer et al. could not be used in the claimed method, there is no evidence of record that the device taught by Cracauer et al. could not be used in the claimed method and Cracauer et al. teaches that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in vitro". The MPEP section 716.01(c), page 700-152 (July 1998) states:

ATTORNEY ARGUMENTS CANNOT TAKE THE PLACE OF EVIDENCE

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Regarding motivation to produce the claimed method, Cracauer et al. teaches that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in vitro".

13. Claims 22-29,31,32,34,35 are rejected under 35 U.S.C. § 103 as being unpatentable June

et al. (WO 94/29436) or June et al. (US Patent 5,858,358) in view of Garra et al.

Regarding the term "regulatory T lymphoid" cells, while it is unclear what said term means or encompasses, in the instant rejection said term will be addressed as encompassing Th1 cells. June et al. teach the method of claim 22, wherein unfractionated T cells or CD4+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody or IL-2 treatment wherein said cells are expanded to at least about 10^9 cells per liter (see abstract, pages 4-9,13, claims 1-28,30-37). Figures 1 and 2 show experimental data indicating the expansion of cells to numbers greater than 10^{10} cells. June et al., page 27, indicates that the cells were maintained at a concentration of 10^6 cells/ml (eg. 10^9 cells/liter). June et al. teach that said cells were treated with IL-2 (eg. see Table 2)). Said treatment leads to the development of Th1 (eg. see claim 28). The cells produced by the method of June et al. include Th1 (eg. as defined by production of IFN-γ (see Table 2). Thus, the method taught by June et al. leads to the production of Th1/ Th1 like cells. June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific cells (see page 9, first complete paragraph) and that said cells can be purified (see pages 29 and 300). T cells are by definition specific for a defined antigen (eg. the antigen bound by the TCR expressed by said T cell). The method of June et al. can use treatment with anti-CD3 and antiCD28 antibodies to generate Th1 cells (eg. see Table 2, wherein said cells produce IFN-γ). June et al. do not teach the method of claim 29. O'Garra et al. teach that stimulation of CD4+ cells in the presence of IL-2 or antiCD3 leads to the development of Th1 cells (eg. see page 460, second column). O'Garra et al. teach that anti-Il-4 antibody treatment of CD4+ cells favors the development of Th1 (see page 460, first column). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because June et al. disclose a method that produces cells with Th1 characteristics, while O'Garra et al. teach that stimulation of CD4+ cells in the presence of IL-2 or antiCD3 leads to the development of Th1 cells and that anti-Il-4 antibody treatment of CD4+ cells favors the development of Th1 (see page 460, first column). One of ordinary skill in the art would have been motivated to do the aforementioned because O'Garra et al. teach that anti-Il-4 antibody treatment of CD4+ cells favors the development of Th1.

14. References not considered on the enclosed IDSs were duplicates of those cited on the

previously filed IDS.

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
January 3, 2000

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600